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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GUNTER, DAVID R

ART UNIT	PAPER NUMBER
1634	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/848,986	Applicant(s) RAZ ET AL.	
	Examiner David R. Gunter	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 1-7 and 9-20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Because of the applicant's election of group II, claims 8-12, drawn to methods of identifying an agent that modulates biological activity of DNA-PK, the application has been transferred to Art Unit 1634. Contact information for the current examiner can be found at the end of this action.

Response to Traversal

The examiner acknowledges the applicant's election with traverse of group II, claims 8-12 in paper number 12, received September 6, 2002. The traverse is on the grounds that a search of the entire application does not represent a serious burden. This argument is not found to be persuasive.

In the restriction requirement sent August 5, 2002 (paper number 11), the claims were divided into the following groups:

1. Group I, claims 1-7, drawn to a method of modulating cell death.
2. Group II, claims 8-12, drawn to a method of identifying an agent that modulates biological activity of DNA-PK.
3. Group III, claim 13, drawn to a composition comprising an agent identified by the method of claim 8.

Claims 14-20 were not addressed in the restriction requirement. A telephone interview with the applicant's attorney (paper number 13, dated November 4, 2002) revealed that the prior examiner had intended that claims 14-20 be included in group I. The examiner agrees that claims 14-20 should be included in group I.

As stated in the prior restriction requirement, the methods of groups I and II are independent and distinct. Inventions are independent and distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the method of group II comprises the modes of operation of adding an agent to a sample containing DNA-PK and detecting an increase or a decrease in the biological activity of DNA-PK. This method can be performed either in a cell-free system (claim 10) or in living cells (claim 12), and can comprise a plurality of measures of DNA-PK activity including DNA binding (claim 9), phosphorylation (claim 11), or production of IL-6 or IL-12 (claim 12). The method of group I comprises the function and effect of modulating cell death in eukaryotic cells, and comprises the method steps of contacting the cells with a known modulator of DNA-PK activity identified by the method of group II or some analogous method. The method of group I further comprises the modes of operation of subjecting cells to hypoxic conditions (claim 6) and assaying the rate of cell death (claims 1-7). Because the methods of groups I and II have substantially different modes of operation, functions, and effects, restriction is deemed proper. A literature search for assays of DNA-PK activity (group II) would not be co-extensive with a search for the role of DNA-PK in cell death, and therefore searching for the methods of both groups represents a significant search burden.

As stated in the prior restriction requirement. The composition of group III is independent and distinct from the method of group I. Inventions are independent and distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, there is no recited relationship between groups I and III. The agent to be used in the method of group I could be identified by numerous methods other than that of group II, and the composition of group III has a plurality of other uses other than the method of group I. For these reasons, groups I and III are considered to be independent and distinct, and restriction is deemed proper. A literature search for the method of group I would not be co-extensive with a search for the composition of group III, and therefore searching both groups represents a significant search burden.

As stated in the prior restriction requirement, groups II and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the agent of claim 13 could have been identified by a plurality of materially different processes including searching for molecules with a chemical structure similar to that of known DNA-PK inhibitors. A literature search for agent of group III would not be co-extensive with a search for the method of groups I and II, and therefore searching for the methods of both groups represents a significant search burden.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for

examination purposes as indicated is proper, and this requirment is made **FINAL**. All non-elected claims, including claims 14-20, are withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 is indefinite because the meaning of the term "cell-based method" is unclear. It is not clear how the term "based" limits or defines the claimed cell-based method. A cell-based method may be interpreted to mean a method in which cells are lysed (e.g. to extract RNA as in Figure 3D) or a method in which the cells remain intact and a secreted protein is measured. Therefore term "cell-based" is indefinite. It is suggested that claim 12 be amended to define the cell-based method as described in the specification.

2. Claims 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 8-12 are drawn to methods for identifying an agent that modulates a biological activity of DNA-PK. However, claim 8 recites that a change in activity of DNA-PK "indicates that the agent modulates a biological activity of DNA-PK." The term "indicates" implies that the alteration in DNA-PK activity suggests an ability to modulate DNA-PK activity, and is not as definitive as the term "identify" recited in the preamble. "Identify" implies a

conclusive demonstration of an agent's ability to modulate DNA-PK. For this reason, the final recited step of the method does not accomplish the objective defined in the preamble, and so it is not clear how agents that modulate biological activity of DNA-PK are to be identified.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller, et al., Blood 92(7):2213-2219, 1998 (hereinafter referred to as "Muller") in view of Finnie, et al, Proc. Natl. Acad. Sci. USA 92:320-324, 1995 (hereinafter referred to as "Finnie") in further view of Lees-Miller et al., Molecular and Cellular Biology 10(12):6472-6481, 1990 (hereinafter referred to as "Lees-Miller") in further view of Han, et al., Journal of Biological Chemistry 271:14098-

14104, 1996 (hereinafter referred to as "Han"). Claim 8 recites a method for identifying an agent that modulates a biological activity of DNA-PK comprising (a) adding an agent to be tested to a sample, the sample comprising DNA-PK and an immunomodulatory nucleic acid molecule under conditions which favor binding of the immunomodulatory nucleic acid molecule to DNA-PK, thereby forming a test sample, and (b) detecting a biological activity of DNA-PK in the test sample as compared to a control sample lacking the agent, wherein an increase or decrease in the biological activity of DNA-PK indicates that the agent modulates a biological activity of DNA-PK.

Muller teaches a nearly identical method for identifying an agent that modulates a biological activity of DNA-PK. In the method of Muller (as described in detail by Finnie, page 320, right column, last paragraph through page 321, left column, first paragraph), DNA-PK is combined with double stranded DNA under conditions that favor binding of the nucleic acid to DNA-PK to form a test sample. An agent to be tested, Chlorambucil is added to the sample and a biological activity of DNA-PK (kinase activity is detected and comparaed to a control sample lacking the agent in order to indicate that the agent modulates biological activity of DNA-PK (Muller, page 2216, figure 2).

Muller does not specifically teach that the nucleic acid molecule to which DNA-PK binds is an immunostimulatory nucleic acid. However, Lees-Miller teaches that double stranded nucleic acid molecules with a variety of sequences and structures stimulate the activity of DNA-PK. Of these, the most effective is an oligonucleotide which contains multiple GC repeats (Lees-Miller, page 6475, figure 3). At the time the application was filed, it was known to those of skill in the art that assays of DNA-PK activity were complicated by the relatively low

abundance of DNA-PK and the presence of multiple kinases that have similar substrate specificity to DNA-PK (Finnie, page 323, right column, second paragraph). It would have been obvious to one of ordinary skill in the art at the time the application was filed to use the poly-GC oligonucleotide taught by Lees-Miller in the assay method of Muller in order to maximize the intensity of the DNA-PK signal to provide an assay method with the highest possible specificity and sensitivity. An oligonucleotide comprising multiple GC repeats was known to those of skill in the art at the time the application was filed to have immunostimulatory effects. Furthermore, an oligonucleotide comprising multiple GC repeats satisfies the definition of immunostimulatory nucleic acid presented in the specification on page 1, paragraph 4.

a. Regarding Claim 9, Muller teaches the embodiment in which the biological activity of DNA-PK is binding to an immunomodulatory nucleic acid molecule oligonucleotides containing GC repeats and plasmid DNA(page 2217, figure 3; sequence of oligonucleotides taught in Han, page 14099, left column, fifth paragraph).

b. Regarding Claim 10, Muller teaches the embodiment in which the method is a cell-free method and the immunomodulatory nucleic acid molecule is detectably labeled (oligonucleotides are labeled with ^{32}P; figure 3, page 2217).

c. Regarding Claim 11, Muller teaches the embodiment in which the biological activity of DNA-PK is activation of DNA-PK kinase activity (page 2216, figure 2).

4. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klinman, et al., Proc Natl Acad Sci USA 93:2879-2883, 1996 (hereinafter referred to as "Klinman") in view of Munoz, et al., Molecular and Cellular Biology 18:5797-5808 1998, (hereinafter referred to as

"Munoz"), in further view of Lees-Miller, in further view of Krieg, et al., Nature 374:546-549, 1995 (hereinafter referred to as "Krieg"). Claim 8 recites a method for identifying an agent that modulates a biological activity of DNA-PK comprising (a) adding an agent to be tested to a sample, the sample comprising DNA-PK and an immunomodulatory nucleic acid molecule under conditions which favor binding of the immunomodulatory nucleic acid molecule to DNA-PK, thereby forming a test sample, and (b) detecting a biological activity of DNA-PK in the test sample as compared to a control sample lacking the agent, wherein an increase or decrease in the biological activity of DNA-PK indicates that the agent modulates a biological activity of DNA-PK. Claim 12 recites the further limitation that the method is a cell-based method and modulation of DNA-PK activity is detected by measuring an amount of IL-6 or IL-12 produced by the cell.

Klinman teaches a method for identifying an agent that modulates the production of IL-6 and IL-12. In the assay method taught by Klinman, immunomodulatory nucleic acid molecules (oligonucleotides containing CpG motifs) were combined with $CD4^+$ T cells, $CD8^+$ T cells, B cells, monocytes, and NK cells to form a test sample. These cell types were known to those of ordinary skill in the art at the time the application was filed to contain DNA-PK (see, for example, Munoz, page 5797, left column, first paragraph). Agents (antibodies against IL-6, IL-12, IFN-gamma, GMCSF, and control antibodies) were added to the test sample and a biological activity (production of IL-6, IL-12, IFN-gamma, and IgM) was detected (Klinman, page 2879, right column, third and fourth paragraphs; also page 2882, figure 4).

Klinman does not specifically teach that the method for treating cells with oligonucleotides containing CpG motifs and measuring the production of IL-6 and IL-12 was an

assay of DNA-PK activity. However, it was known to those of ordinary skill in the art at the time the application was filed that oligonucleotides containing CpG motifs were potent activators of DNA-PK (Lees-Miller, page 6475, figure 3). Because treatment of cells with oligonucleotides containing CpG motifs resulted in both an activation of DNA-PK and secretion of IL-6 and IL-12, it would have been obvious to one of ordinary skill in the art to use IL-6 and IL-12 production as an indirect measure of DNA-PK activation by oligonucleotides containing CpG motifs. One of ordinary skill in the art would have been motivated to use IL-6 and/or IL-12 production as an indirect measure of DNA-PK activity because at the time the application was filed it was known that assays of DNA-PK activity were difficult to perform due to the relatively low abundance of DNA-PK and the presence of multiple kinases that have similar substrate specificity to DNA-PK (Finnie, page 323, right column, second paragraph). Assays for secreted IL-6 and IL-12, however, were readily carried out using established ELISA methods (Klinman, page 2879, left column, fifth paragraph). The ease of measurement of IL-6 and IL-12 would have provided sufficient motivation to one of ordinary skill in the art to use the method of Klinman as an assay of DNA-PK activity.

Conclusion

5. **No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

David R. Gunter, DVM, PhD
November 14, 2002

B. J. FORMAN
PATENT EXAMINER